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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/012,194	12/06/2001	Manuela Martins-Green	407B-914500US	5287

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[REDACTED] EXAMINER

QIAN, CELINE X

[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1636

DATE MAILED: 09/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/012,194	MARTINS-GREEN ET AL.
	Examiner	Art Unit
	Celine X Qian	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM
 THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 04 June 2004.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 2-6,9-20,23,25,26 and 43-45 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 2-6,9-20,23,25,26 and 43-45 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on 04 June 2004 is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____. | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Claims 2-6, 9-20, 23, 25, 26 and 43-45 are pending in the application.

This Office Action is in response to the Amendment filed on 6/4/04.

Response to Amendment

The objection to claim 23 has been withdrawn in light of applicant's amendment of the claim.

The rejection of claims 1-4, 6, 7, 11, 12, 15, 18-20, 25 and 26 under 35 U.S.C.102 (b) has been withdrawn in light of applicant's amendment of the claims.

Claims 2-6, 9-20, 23, 25, 26 and 43-45 stand under 35 U.S.C.112 1st paragraph for reasons set forth of the record mailed on 12/31/03 and further discussed below.

Claims 2-6, 9-15, 18-20, 23, 25, 26 and 43-45 are rejected under 35 U.S.C.103 (a) for reasons discussed below.

Drawings

The drawings filed on 6/4/04 is objected to for containing new matter. Figure 11 is not acceptable because it is not present in the original specification, therefore, it constitutes new matter.

Response to Arguments

Claim Rejections - 35 USC § 112

Claims 2-6, 9-20, 23, 25, 26 and 43-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an artificial tissue comprising endothelial cells separating two layers of support matrix comprising connective tissue, optionally epithelial cells on top of the second supporting matrix, wherein the artificial tissue comprises one or more

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microvessels produce therein, and said microvessel produces mononuclear leukocytes, does not reasonably provide enablement for such an artificial tissue, wherein the microvessel produces any blood cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In response to this rejection, Applicants argue that the specification teaches that the claimed artificial skin can produce mononuclear leukocytes in the example given in Appendix A. Applicants thus conclude that the specification fully enables the claims.

Applicant's argument has been fully considered and deemed partially persuasive. As such, the claimed invention is enabled to the scope of the artificial skin with microvessels that produces mononuclear leukocytes. As discussed in the previous office action, hematopoietic stem cells are ultimately responsible for the constant renewal of blood *in vivo*. Such hematopoietic stem cells are found in adult bone marrow, peripheral blood and umbilical cord blood. The claimed artificial tissue does not comprise cells of hematopoietic origin. Although the specification demonstrates the endothelial cells can differentiated into mononuclear leukocytes *in vitro*, the specification fails to demonstrate that the artificial skin can produce any other types of blood cells in such an *in vitro* setting. Therefore, whether the microvessels produce in the claimed artificial tissue can produce any blood cells is unpredictable. As such, the claimed invention is not enabled to the full scope, and this rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Black et al., in view of Li et al (2000, PNAS, Vol.275, No.45, pages 35384-35392).

Black et al. teach a skin equivalent preparation comprising human keratinocytes plated on endothelial dermal equivalent or endothelial fibroblast dermal equivalent mixed with collagen (see page 1333, 1st col., 2nd and 3rd paragraph). Black et al. also teach that the endothelial fibroblast dermal equivalent comprising fibroblast and HUVEC (see page 1333, 1st col., 2nd paragraph). Black et al. further teach that a network of capillary-like tubular structures is formed in the tissue (see page 1333, 2nd col., 3rd and 5th paragraph). Furthermore, Black et al. teach that said tissue produces laminin, type IV collagen and extracellular matrix (see page 1334, 1st col., 2nd paragraph, and Figures 1, 2 and 3). Moreover, Black et al. disclose that said tissue is self maintained *in vitro*, and is suitable for tissue graft (see page 1338, entire 1st col., and 2nd col., 2nd paragraph). However, Black et al. do not teach the artificial tissue comprising Vitrogen.

Li et al. teach that Vitrogen, a trademark name for type I collagen, is purchased from Collagen Corp.

It would have been obvious to one of ordinary skill in the art to use Vitrogen to make the artificial tissue as claimed based on the teaching of Black et al. and Li et al. Since Black et al.

teach a method of making an artificial skin equivalent as claimed using collagen (see page 1333, 1st col., 2nd paragraph), and Li et al. teach such collagen can be purchased from Collagen Corp. for the trademark name of Vitrogen, one of ordinary skill of art would just purchase Vitrogen to use in the method of making an artificial skin equivalent for the ease of making said tissue. One of ordinary skill in the art would have reasonable expectation of success because the method has already been taught by Black et al., and Vitrogen is available for purchase at the time of the invention was made. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 2-6, 11, 12, 15, 18-20, 23, 25, 26, 43 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Black et al., in view of Montesano et al (IDS).

The teaching of Black et al. is discussed above. However, Black et al. do not teach an artificial tissue comprising two layers of support matrix-connective tissue mixture separated by a layer of endothelial cells.

Montesano et al. teach endothelial cell monolayers established on the surface of collagen matrix and covered with another layer of collagen matrix induces the endothelial cells to reorganize into a network of branching and anastomosing capillary-like tubes resembling capillary beds *in vivo* (see page 1649, 2nd col., 3rd paragraph, lines 1-4). Montesano et al. further teach that an appropriate topological relationship of endothelial cells with collagen matrices, similar to that occurring *in vivo*, has an inductive role for endothelial cells to form vessel-like structures *in vitro* (see abstract).

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It would have been obvious to one of ordinary skill in the art to make an artificial skin equivalent as taught by Black et al. and introduce a second layer of connective tissue on top of the endothelial cell based on the teaching of Montesano et al. One of ordinary skill in the art would have been motivated to do so because it would resemble the capillary bed *in vivo* and thus induce capillary formation closely resemble that of *in vivo* setting, as demonstrated by Montesano et al. The level of skill in the art is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to make an artificial skin equivalent as taught by Black et al., and introduce a second layer of connective tissue on top of the endothelial cells. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Black et al., in view of Montesano et al., and Li et al.

The teachings of Black et al. Montesano et al. and Li et al. are discussed above. Black et al. and Montesano et al. do not teach making an artificial tissue using Vitrogen.

The obviousness of making an artificial tissue comprising two layers of connective tissue separated by a layer of endothelial cells is discussed above. Both Black and Montesano teach using collagen as support matrix. Since Vitrogen is a trademark for collagen commonly used in cell culture, one of ordinary skill in the art would just purchase it and use it in the experiment making the artificial tissue. The level of skill in the art is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success because the method has already been taught by Black et al. and Montesano et al., and Vitrogen is

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available for purchase at the time of the invention was made. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 2, 10, 23 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Black et al., in view of Montesano et al., and Lokeshwar et al (2000, JBC, Vol.275, No.36, pages 27641-27649).

The teachings of Black et al. Montesano et al. are discussed above. However, Black et al. and Montesano et al. do not teach making an artificial tissue using endothelial cells comprise primary human adult lung microvascular cells.

Lokeshwar et al. teach that primary human endothelial cell culture is established by culturing human lung microvessel endothelial cells (hMEVC-L) purchased from Clonetics/BioWhittaker Inc.(see page 27642, 1st col., 4th paragraph, lines 1-3).

The obviousness of making an artificial tissue comprising two layers of connective tissue separated by a layer of endothelial cells is discussed above. It would have been obvious to one of ordinary skill in the art to use hMVEC-L to make the artificial skin equivalent as taught by Black et al. and Montesano et al. One of ordinary skill in the art would have been motivated to do so for the ease of the experiment, since purchasing hMVEC-L would skip the step of isolating the endothelial cells. Since Black et al. and Montesano et al. demonstrate that both HUVEC and bovine adrenal cortex microvascular cells can form capillary structure *in vitro* when made into artificial skin, one of ordinary skill in the art thus would have reasonable expectation of success to replace HUVEC used by Black with hMVEC-L to make the artificial skin equivalent.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.

